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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,073	12/13/2001	Yiyou Chen	GC713	5600

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 01/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,073	CHEN ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2003 and 05 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-21 and 23-37* is/are pending in the application.

4a) Of the above claim(s) *19-21 and 35-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-18 and 23-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's responses of October 2, 2003 and November 5, 2003 to the first Office Action on the Merits of this case is acknowledged. It is acknowledged that applicants have amended Claims 1, 2, 7-9, 23, 24, 29, and 30 and cancelled Claims 12 and 22. Claims 19-21 and 35-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 1-11, 13-18, and 23-34 are hereby reconsidered.

Specification-Objections

Objection to the specification for citing priority in the first paragraph to a provisional application by the Attorney Docket number, GC684-20, is maintained, as no corrections have been made.

Objection to the specification because the font for the temperature symbol (^{o}) is incorrect is maintained, because no corrections have been made.

Objection to the specification for having an incomplete parenthesis on 94, line 24, is maintained, because no corrections have been made.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-18, and 23-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Rejection of Claims 1-11, 13-18, and 23-34 under 35 U.S.C. 112, second paragraph, as described in the prior action, is maintained. It acknowledged that Applicants have amended the claims such that, a variant sequence can consist of 1-50 residues of pre-targeted enzyme being mutated. However, Claims 1-11, 13-18, and 23-34 are still indefinite because, it is unclear how to distinguish between a single variant sequence, two variant sequences, or three variant sequences etc. For example (bold indicates changes).

Native: NH_2-AA_x–GKADIAANKPVTPQTLFELGSISKTFTGV– AA_x-COOH

Variant: NH_2-AA_x–G**RIEL**AANKPVTPQTLF**DV**GS**L**SKTFTGV– AA_x-COOH

Does said variant contain a single variant sequence, two variant sequences, or three variant sequences? Because a variant sequence can be any length, between one and 50 residues, and contain any number of amino acid residues inserted, deleted, substituted, or replaced, it is not possible to determine the metes and bound of a single variant sequence or to distinguish the boundaries between adjacent variant sequences. For these reasons, rejection of Claims 1-11, 13-18, and 23-34 under 35 U.S.C. 112, second paragraph, as described in the prior action, is maintained.

Claims 1-11, 13-18, and 23-34 are indefinite in reciting: "the variant sequence was not known to bind to the target independently of the targeted enzyme", as what is "known" is changeable over time.

Claims 1-11, 13-18, and 23-34 are unclear in reciting: "greater than 1% of the pre-targeted enzyme". It is suggested to amend to: "greater than 1% of the catalytic activity of the pre-targeted enzyme".

Claims 2, 7-9, 23, 24, 29, and 30 are further rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Claims 2, 7, 8, 23, and 24 (section i) are confusing and unclear in reciting: "...the variant sequence being derived from variation-tolerant sequence, wherein the... the variation-tolerant sequences being of a corresponding pre-targeted enzyme,". It is believed that claim is meant to recite: "...the variant sequence being derived from variation-tolerant sequence derived from a corresponding pre-targeted enzyme, wherein...". Correction is requested.

Claims 24, 29 and 30 (section i) are confusing and unclear in reciting: "...the variant sequence being derived from variation-tolerant sequence, ... the variation-tolerant sequences being of a corresponding pre-targeted β-lactamase enzyme,". It is believed that claim is meant to recite: "...the variant sequence being derived from variation-tolerant sequence derived from a corresponding pre-targeted β-lactamase enzyme, wherein...". Correction is requested.

Claim 9 is unclear in reciting: "...wherein the variant-sequence comprises at least two variant sequences". Is the claim meant to recite: "...wherein the targeting sequence comprises at least two variant sequences"?

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of Claims 1-11, 13-18, and 23-34 under 35 U.S.C. 112, first paragraph for lack of enablement, as described in the prior action, is maintained.

Claims 1-11, 13-18, and 23-34 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the β-lactamase (pdb accession # 1bls) with a target site for streptavidin in the B-loop, made as described on page 89 line 28-page 91 line 6, does not reasonably provide enablement for any active targeted enzyme comprising a targeting site that binds a target wherein the targeting site comprises a variant sequence and wherein the variant sequence was not known to bind to the target independently of the targeted enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 2, 7, 8, 23, 24, 29, and 30 are so broad as to encompass any active targeted enzyme comprising a targeting site that binds a target wherein the targeting site comprises a variant sequence and wherein the variant sequence was not known to bind to the target independently of the targeted enzyme. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of targeted enzymes broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired targeted enzyme activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to a β-lactamase with a targeting site of streptavidin.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 1, 2, 7, 8, 23, 24, 29, and 30, which encompass any active targeted enzyme comprising a targeting site that binds a target wherein the targeting site comprises a variant sequence and wherein the variant sequence was not known to bind to the target independently of the targeted enzyme. The specification does not support the broad scope of Claims 1, 2, 7, 8, 23, 24, 29, and 30 because the specification does not establish: (A) any pretargeted enzymes that can be modified to make an active targeted enzyme comprising a targeting site that binds a target wherein the targeting site comprises a variant sequence and wherein the variant sequence was not known to bind to the target independently of the targeted enzyme; (B) the general tolerance, and extent of such tolerance, of the enzymatic activity of any pretargeted enzyme to modification as an active targeted enzyme wherein the variant sequence of the targeting site was not known to bind to the target independently of the targeted enzyme; (C) a rational and predictable scheme for modifying, with an expectation of obtaining the desired biological function, any enzyme into an active targeted enzyme comprising a variant targeting site that was not known to bind to the target independently of the targeted enzyme; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible

choices of enzymes having variant targeting sites, that are not known to bind to the target independently of the targeted enzyme, are likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a large number of active targeted enzymes comprising a targeting site that binds a target wherein the targeting site comprises a variant sequence and wherein the variant sequence was not known to bind to the target independently of the targeted enzyme. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 3-6, 9-11, 13-18, 25-28, and 31-34, as dependent on Claims 1, 2, 7, 8, or 23, 24 are rejected under 35 U.S.C. 112, first paragraph for lack of enablement for the same reasons.

In support of Applicant's request that rejection of Claims 1-11, 13-18, and 23-34 under 35 U.S.C. 112 first paragraph, for lack of enablement, be withdrawn, they provide the following argument. "These rejections...are believed moot in view of the amendments presented herein." This argument is not found to be persuasive, as the claims have not been amended to encompass a scope that is supported by the specification.

Rejection of Claims 1-11, 13-18, and 23-34 under 35 U.S.C. 112, first paragraph, for insufficient written description, as described in the prior action, is maintained.

Claims 1-11, 13-18, and 23-34 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of targeted enzymes comprising a targeting site that binds a target wherein the targeting site comprises a variant sequence and wherein the variant sequence was not known to bind to the target independently of the targeted enzyme. Recitation of the limitation "wherein the variant sequence was not known to bind to the target independently of the targeted enzyme" introduces new matter into the disclosure, as the specification fails to describe any representative species of such targeted enzymes. Furthermore, given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

In support of Applicant's request that rejection of Claims 1-11, 13-18, and 23-34 under 35 U.S.C. 112, first paragraph, because of insufficient written description, be withdrawn, they provide the following argument. "These rejections...are believed moot in view of the amendments presented herein." This argument is not found to be persuasive, as the claims have not been amended to recite only targeted enzymes that are sufficiently described by the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejection of Claims 1, 12, 14, 16, and 17 under 35 U.S.C. 102(b) as being anticipated by Nakanishi et al, 1997, for the reasons presented in the prior action, is maintained.

In support of Applicant's request that rejection of Claims 1, 12, 14, 16, and 17 under 35 U.S.C. 102(b) be withdrawn, they provide the following argument. "As amended, the present claims recite that "...the catalytic activity of the targeted enzyme is greater than at least 1% of the pretargeted enzyme". Nakanishi et al do not teach a catalytic activity greater than 1% (e.g., the catalytic activity kcat/Km of the T38D mutant ("targeted" enzyme is decreased by two-orders of magnitude with the cognate, that is, naturally occurring, cofactor NADPH and over 3-orders of magnitude for NADP as a cofactor (see, Table 1)."

This argument is not found to be persuasive for the following reasons. It is acknowledged that the affinity of the enzyme for the cofactors is dramatically altered. However, said analysis is not reflective of the "activity" of the enzyme, as recited in the instant claims. The Km and kcat/Km for the substrate, not the cofactor, are the important data in assessing enzyme activity. The data of Table 1 demonstrates that upon mutation of the enzyme, the Km for the substrate P3A, in the presence of the NADPH cofactor, was shifted from 17μM to 580μM, while the kcat/Km was shifted from $69s^{-1}mM^{-1}$ to $4s^{-1}mM^{-1}$. In the presence of the NADH cofactor, the activity of the enzyme for the substrate P3A was shifted from a Km of 480μM to 230μM, while the kcat/Km was shifted from $3.6s^{-1}mM^{-1}$ to $14s^{-1}mM^{-1}$. Therefore, the

enzyme retained more that 1% enzymatic activity, when the targeting site for cofactor was altered.

Rejection of Claims 1-3, 5-7, 9, 10, and 12-17 as being anticipated by Maier et al, 1999 and rejection of Claims 1 and 15-18 as being anticipated by Vrudhula et al, 1993 or Meyer et al, 1992 are withdrawn as, the specification specifically excludes N- and C-terminal fusion proteins from the scope of the invention (page 27, lines 23-26).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 23-25, 31, and 33 under 35 U.S.C. 103(a) as being unpatentable over Verdet et al, 1999 in view of Maier et al, 1999, Vrudhula et al, 1993 or Meyer et al, 1992 and further in view of Barthelemy et al, 1992 is withdrawn because, as described above, the targeted enzymes of Maier et al, Vrudhula et al, and Meyer et al, 1992 are N-terminal or C-terminal fusions proteins, which are not encompassed by the scope of the disclosed invention.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943 (571-272-0943 after January 12, 2004). The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.

REBECCA E. PROUTY
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1600